In the first lines of claims 15 and 16, please delete "oligomer" and insert --compound-- therefor.

REMARKS

Claims 9-10 and 15-16 are pending in this patent application.

As a preliminary matter, Applicants' undersigned attorney wishes to thank Examiner Kunz for taking the time to meet with him and Mr. Herb Boswell for the interview held June 7, 1994. At that interview the Examiner was presented with a copy of Keller *et al.*, reference (Keller, *et al.*, *Helvetica Chimica Acta*, **1993**, *76*, 884, acknowledged on the interview summary form of this same date). A formal copy of Keller, *et al.* is being submitted herewith.

The Office Action mailed April 7, 1994, acknowledged the submission of a new Abstract but alleged that the new Abstract "still lacks specificity." (Office Action at page 2). Applicants believe that the earlier-filed Abstract was sufficiently specific, but have amended the Abstract to even more clearly describe the claimed invention.

Claims 9-10 and 15-16 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an adequate written description of the invention and for failing to adequately teach how to use the invention. The Office Action asserts that the claims are unduly broad because they include

peptide-containing and saccharide-containing oligomers. Applicants believe that the claims, as filed, accurately describe the invention. However, to expedite prosecution, the claims have been amended to recite preferred embodiments of the invention wherein the T_3 and/or T_5 groups are nucleotides.

With respect to the assertion that the Specification exemplifies only 2'-allyl guanosine as a modified nucleotide, Applicants respectfully disagree. The Specification teaches persons skilled in the art much more than 2'-allyl guanosine as the sole type of modified nucleotide. The Specification on pages 3 and 5-16 teaches 2'-O-modified guanosine nucleotides and 2'-O-modified diaminopurine nucleotides, wherein the 2'-O-modification comprises C_3-C_{20} alkyl, C_4-C_{20} alkenyl, and C_2-C_{20} alkynyl derivatives. In addition, Examples 1-48 of the Specification clearly teach the preparation of 2'-O-alkylated, 2'-O-(N-phthalimido) alkylated, and 2'-O-(N-imidazol-1-yl) alkylated compounds. In addition, Applicants clearly teach that compounds of Formulas I, II, and III can be prepared by alkylation effected directly on 2,6-diamino-9-(β-*D*-ribofuranosyl)purine with an appropriate compound having the formula R_1-L, wherein R_1 is C_3-C_{20} alkyl, C_4-C_{20} alkenyl or C_2-C_{20} alkynyl and L is a leaving group, in the presence of a base of sufficient strength to effect removal of the proton from the 2' hydroxyl of the ribofuranosyl sugar moiety of 2,6-diamino-9-(ß-*D*-ribofuranosyl)purine (*see, e.g.*, Specification at pages 11-12). Applicants further teach

the reagents required to prepare such compounds (*See, e.g.*, Specification at pages 12-14). In summary, Applicants teach persons of ordinary skill in the art how to prepare a wide variety of 2'-O-modified nucleotides and oligonucleotides. Accordingly, Applicants request that the rejection of claims 9-10 and 15-16 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 9-10 stand rejected under 35 U.S.C. § 103 as being unpatentable over Cotten, *et al.*, *Nucleic Acids Research* **1991**, *19*, 2629. The Office Action asserts that "[t]he only difference between the 2'-O-ethyl and the 2'-O-methyl oligomers disclosed by Cotten et al. and those encompassed by the claims is a single halogen atom on the methyl or ethyl moiety." (Office Action at page 3). Applicants respectfully request reconsideration of this rejection, particularly in view of the proposed amendments to the claims, for several reasons. For example, the Office Action is incorrect in its assertion that the claimed compounds differ from those disclosed by Cotten, *et al.* only with respect to the inclusion of a fluorine atom. Applicants have amended Claim 9 to exclude the 2'-O-methyl and 2'-O-ethyl compounds disclosed by Cotten, *et al.*, and Cotten, *et al.* nowhere disclose or suggest the remaining 2'-O-substituted compounds recited in claim 9, such as 2'-O-alkenyl and 2'-O-alkenyl substituted compounds. Also, whereas claim 10 is directed to 2,6-diamino-9-(β-*D*-ribofuranosyl)purines, Cotten, *et al.* merely describe 2'-O-substituted adenosine, guanosine,

cytidine and uridine. Cotten, *et al*. do not teach or suggest 2,6-diamino-9-(β-*D*-ribofuranosyl)purines, much less modifying such compounds to include a 2'-O-substituent.

Additionally, the Cotten, *et al*. reference does not disclose or suggest how one would synthesize the few compounds it discloses. For example, the Cotten, *et al*. reference on page 2630 refers to footnote 16 for a description of the synthesis of 2-O'-methyl and 2'-O-ethyl nucleotides. Footnote 16, in turn, refers to a "manuscript in preparation." A "manuscript in preparation" is one that has not even been accepted for publication, let alone published and available to the art skilled. As was noted at the interview, 2'-O- guanosine compounds, such as those allegedly disclosed by Cotten, *et al*., are inherently difficult to prepare. Indeed, the Keller, *et al*. reference demonstrates that such difficulties were still being encountered nearly two years after publication of the Cotten, *et al*. reference. For example, the Keller, *et al*. reference notes that although a number of groups can theoretically be attached to the 2'-position of nucleosides, "selective reaction at the 2'-hydroxy group of ribose is difficult, and efficient alkylations can only be achieved with very reactive electrophiles." (page 884, ¶ 2). In view of the difficulties inherent in preparing compounds such as suggested by the Cotten, *et al*. reference and the reference's failure to provide any synthetic methodology, it cannot reasonably be said that the Cotten, *et al*. reference

renders the claimed 2'-O-substituted guanosine compounds obvious. Indeed, in view of the recognized difficulties in preparing such compounds, persons of ordinary skill the art skilled would find Applicants' invention surprising and non-obvious.

Thus, for the reasons noted above, reconsideration of the rejection of claims 9 and 10 in view of the Cotten, *et al.* reference is respectfully requested.

Claims 15 stands rejected under 35 U.S.C. § 103 as being unpatentable over Iribarren, *et al.*, *Proc. Natl. Acad. Sci. USA*, **1990**, *87*, 7747. The Office Action asserts that the Iribarren, *et al.* reference suggests the use of a 2'-O-modification having four carbon atoms, and that this limited disclosure renders the entirety of claim 15 obvious. Applicants respectfully request reconsideration, as Iribarren, *et al.* nowhere disclose or suggest the claimed compounds -- 2'-O-derivatives of guanosine.

Noticeably absent from the 2'-O-substituted compounds disclosed by Iribarren, *et al.* are guanosine compounds. The only structure shown in the Iribarren, *et al.* reference is that of cytidine, a pyrimidine nucleoside. (*see, e.g.*, structures on page 7747, column 2), not guanosine, a purine nucleotide. Iribarren, *et al.* nowhere disclose or suggest a 2'-O-substituted guanosine. The sequence of the 2'-O-alkyl oligonucleotides (oligonucleotides B and C) of the testing procedures given in Iribarren, *et al.* is listed in the last line of the caption of Fig. 2 on page 7748.

Although the sequence contains multiple nucleotide units of the other three common nucleotides (*i.e.*, A, C and U), it is devoid of G nucleotides. As recognized by persons of ordinary skill, the synthesis of guanosine derivatives presents special difficulties. For example, Robins, *et al.*, *Can. J. Chem.* **1981**, *59*, 3360 (copy enclosed) acknowledge that although "convenient and high yield methods have been devised for synthesis of the 2'-O- and 3'-O-methyl ethers of adenosine, cytidine, and uridine .... guanosine has presented significant difficulties." (page 3360, column 1). As demonstrated by the above-noted Keller, *et al.* reference, these difficulties were still being encountered well after the filing date of the present application. The Iribarren, *et al.* reference fails to address the difficulties inherent in guanosine nucleotide synthesis, much less how they could be overcome. Thus, the reference cannot reasonably be said to render the claimed compounds obvious.

Claim 16 also stands rejected for alleged obviousness in view of the Iribarren, *et al.* reference. Applicants request reconsideration of this rejection for the reasons set forth above for claim 15, since the Iribarren, *et al.* reference fails to disclose or suggest the guanosine-containing compounds to which claim 16 is directed.

Moreover, claim 16 is independently patentable over the Iribarren, *et al.* reference in that the reference specifically teaches away from 2'-O-substituents having five or more carbon

atoms. For example, at page 7749, column 1, the reference states that:

> Our data indicate that the 2'-O-(3,3-dimethylallyl) oligoribonucleotides are unable to form stable hybrids with complementary RNA target sequences (Fig. 4 and data not shown).

It is further stated on page 7749, column 2 that:

> Additional experiments showed little U2 snRNP binding with a 5'-end-labeled 2'-O-(3,3-dimethylallyl) oligoribonucleotide, again indicating that it is unable to form stable hybrids with complementary target sequences (data not shown).

And on page 7750, column 2, Iribarren, *et al.* summarize their findings by stating that substituents having only three or four carbon atoms should be used:

> Since a five-carbon 2'-O-alkyl group in an antisense oligoribonucleotide markedly inhibits binding to complementary RNA sequences, future attempts to prepare alkylated RNA probes that are superior to the 2'-O-allyl oligoribonucleotides should concentrate on either four-carbon or alternative three-carbon groups.

Thus, the teaching of the Iribarren, *et al.* reference -- that substituents having five or more carbon atoms produce unsatisfactory results and should be avoided -- would lead persons of ordinary skill in the art away from the claimed invention. The Office Action, however, alleges that persons of ordinary skill would have recognized that the unsatisfactory results achieved by Iribarren, *et al.* were attributable to the authors' use of a branched five-carbon substituent. For example, Office Action asserts that "the artisan would have deemed it likely that an unbranched five-carbon atom modification would

have permitted proper hybridization" (Office Action at page 5) and that "[i]t was probably the branching rather than the number of carbons atoms that interfered with proper hybridization." (Office Action at page 6). Significantly, however, there is no evidence of record supporting either of these assertions. Indeed, the only art of record, the Iribarren, *et al.* reference, provides a contrary teaching. The Iribarren, *et al.* reference teaches that five-carbon 2'-O-alkyl groups should be avoided, not that some five-carbon groups are acceptable but that others should be avoided:

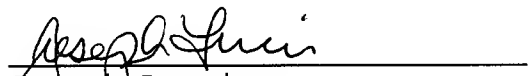
> Longer alkyl groups are likely to pose serious solubility and aggregation problems, even if the use of unbranched chains would circumvent the inhibition of hybrid formation observed with 3,3-dimethylallyl.

(page 7750, column 2). It is only through improper use the hindsight provided by Applicants' disclosure that the benefits of relatively large 2'-O-substituents can be discerned. The fact that the Iribarren, *et al.* authors -- all of whom presumably qualify as "persons of ordinary skill" -- did not attempt to use unbranched five-carbon groups (but, instead, abandoned five-carbon groups entirely in favor of three-carbon and four-carbon groups) is compelling evidence that persons of ordinary skill would not have considered the Examiner's proposed modification obvious. *In re Rosenberger*, 156 U.S.P.Q. 24 (C.C.P.A. 1967) (discovery of an invention in the face of prior art which

suggests that such a invention would produce unacceptable results is the antithesis of obviousness).

In view of the foregoing, Applicants submit that the claims presently before the Examiner patentably define the invention over the applied art and are otherwise in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,



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